

## RATIONALE FOR CLINICAL INTERVENTIONS IN PRODROMAL PSYCHOSIS. ARE SUCH INTERVENTIONS SAFE?

Mark Agius<sup>1,2,3</sup> & Sophie Butler<sup>4</sup>

<sup>1</sup>Department of Psychiatry University of Cambridge, Cambridge, UK

<sup>2</sup>Clare College Cambridge, Cambridge, UK

<sup>3</sup>South Essex Partnership University Foundation Trust, UK

<sup>4</sup>Foundation School Eastern Deanery, UK

### SUMMARY

We compare the reported side effects of medication from the trials of prodromal psychosis treatment. We note that the side effects of antipsychotics are those described in the usual pharmacology of these substances and that the severity of side effects are dependent on dosage, with more side effects at higher doses. We report on the search for alternative compounds for the treatment of prodromal psychosis. Omega fatty acids and Cognitive Behavioural Therapy are certainly good adjuvant treatments for suspected prodromal psychosis. With further evidence they may be considered appropriate to use as monotherapy, particularly in the early prodrome. Treatment of prodromal psychosis continues to present a number of risks; therefore the decision to treat ultimately must depend on the symptoms presented by the individual.

**Key words:** prodrome - at ultra high risk mental state – antipsychotics – antidepressants – apoptosis - plasticity

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### INTRODUCTION

There continues to be debate about the safety and advisability of treating the prodrome of psychotic illness since the publication of McGorry's landmark study in 2002 (McGorry 2002). Such discussion focuses on the side effects of medications and the safety of treating the developing brain with antipsychotics (Bentall 2002). The prefrontal cortex continues developing up to the age of 25, pertinently many of the patients who present with a potential diagnosis of prodromal psychotic illness are under the age of 25.

The uncertain natural history of prodromal symptoms makes the decision to initiate treatment even more controversial. In a prodromal situation there is the possibility that some patients may never convert to having a full blown psychotic illness. This is not necessarily because they are 'false positives', but because some patients with prodromal symptoms may simply revert to normal.

In this paper we will attempt to critically review the literature on different treatments of prodromal psychosis in order to assess which treatment options are the safest to consider.

### RATIONALE FOR CLINICAL INTERVENTIONS IN PRODROMAL PSYCHOSIS

The rationale for treating patients in the prodrome of a psychotic illness is to attempt to prevent the illness from developing and hence to return the patient to normal functioning. There has been major debate in the literature about the ethical issue of treating prodromal

patients with antipsychotics (Bentall 2002). The potential for harm with antipsychotics must be balanced the risks of not treating a patient in the prodrome. If no treatment is provided then many prodromal patients are destined to develop a full-blown psychotic illness, with important consequences for an individual's health and their future life (Agius 2008).

The provision of appropriate intervention is dependent on the identification of those individuals who would benefit from treatment and the identification of effective interventions that change the course of the disease.

### IDENTIFICATION OF PATIENTS AT RISK FOR PSYCHOSIS

If the prodrome can be recognised then it may be possible to interrupt progression to psychosis, or to facilitate rapid treatment upon its emergence. The prodrome of a psychotic illness is a period of non-psychotic disturbance in experience or behaviour that precedes the emergence of psychotic symptoms.

The prodromal features of psychosis most commonly described include:

- reduced concentration and attention;
- reduced drive and motivation;
- anergia;
- depressed mood;
- sleep disturbance;
- anxiety;
- social withdrawal;
- suspiciousness;
- deterioration in role functioning;
- irritability.

These symptoms are quite non-specific and they will vary in intensity as the illness progresses, hence it is necessary to properly assess these patients using a technique which has been devised to assess both the presence of symptoms and their intensity. This will inform the clinician about the likelihood of the patient shortly developing full psychosis (referred to a 'Ultra High Risk of Psychosis'). One such technique is to use a structured interview such as the CAARMS (Singh 2005), this assessment should help to determine the treatment, and in particular when to intervene.

The problem of identifying patients who would benefit from intervention is compounded by two further facts. The first is the lack of evidence for a predictable natural history of prodrome conversion to full psychotic illness. Conversion rates have fallen over the period in which trials have been carried out from 40% at six months, and 50% at one year in 1998 (Yung 1998) to 7.1-9.1% in Yung and McGorry's latest report in 2011 (Yung 2011).

The second fact is that the distinction between a prodromal patient who is at 'ultra-high risk' of developing a full psychosis and a patient newly diagnosed as fully psychotic is in fact an artificial dividing line. This is decided on the basis of a score on a rating scale such as CAARMS, rather than a distinct physical fact. Symptoms instead grow incrementally to the point of full psychosis (Singh 2005), with the consequence that 'a recently advanced hypothesis posits that the long-term harm caused by psychosis occurs principally in the first few months or even weeks after the onset of psychosis' (Marshall 2005).

## IDENTIFICATION OF EFFECTIVE INTERVENTIONS

The literature describes three main groups of intervention that have the potential to alter the progression of the prodrome to full psychosis.

### Antipsychotics

Most of the published trials are those using atypical antipsychotics. It is the safety of these medications which have been called into question and will be discussed in more detail later. These trials show evidence of reducing conversion to full psychosis. For the effectiveness of the individual trials, we refer you to the trials themselves, and our previous metanalysis (Agius 2008, Kelly 2010, Holt 2011). Suffice to say that combinations of low dose risperidone and CBT, as well as amisulpride and aripiprazole have been shown to be effective. A study of olanzapine did not in fact reach statistical significance.

Due to the controversy of using antipsychotics and causing potential harm it is important to assess the reality of the evidence on side effects reported from the trials. All these trials are small but an evaluation of this data is the best we can currently do to assess whether

there are likely to be serious effects as a consequence of treating the developing brain with atypical antipsychotics.

### Medications aimed at modifying brain alterations

The issue of risk versus benefit would be partially resolved if it were possible to provide other means of effectively treating prodromal psychosis with fewer risks than antipsychotic medications. MRI findings have shown loss of grey matter during the prodromal period; in 2005, Singh et al commented that 'A recent report that specific brain changes accompany prodromal decline and predate the emergence of frank psychosis, if replicated, will provide compelling justification for intervening in the prodromal phase (Pantelis 2003)'. In fact these findings have been replicated by scientists in Munich (Koutsouleris 2009, Meisenzahl 2008, Meisenzahl 2008).

Hence legitimate targets for prevention of psychosis are medications or other forms of treatment which will prevent abnormal changes in plasticity, abnormal apoptosis and consequent loss of grey matter during the prodromal phase of the illness. Many such compounds have been considered (Berger 2007). These include antidepressants, omega-3 fatty acids, low dose lithium, modulators of glutamateric neurotransmission (e.g. ampakines, glycine, memantine), erythropoietin, N-acetylcysteine, COX-2 inhibitors or antioxidants.

Clinical trials suggest that monotherapy with antidepressants, omega-3 fatty acids or low-dose lithium was able to improve symptoms and functioning, and delay or in some cases even prevent the onset of frank psychosis. These therefore may be considered as alternatives to antipsychotics. The main problems with some of these trials is the overall lack of evidence and also their short duration; for instance, the main trial of omega-3-fatty acids only lasted 3 months.

### Psychological Interventions

It needs to be noted that medical and psychological treatments for prodromal psychosis are not mutually exclusive. It is reasonable to employ both types of treatment, as McGorry and Yung have done (Yung 2011, McGorry 2002). It is also reasonable that studies should be carried out in order to assess the effect of CBT alone, as Bentall had suggested (Bentall 2002) and of medication alone, as is the case with the olanzapine studies (Woods 2007, McGlashan 2003, McGlashan 2006). It is of interest that the German studies have posited that CBT can be used in the early prodrome, and medication used in the later phase of the prodrome, or at Risk Mental State (Bechdolf 2007, Ruhrmann 2007). It however seems to the present authors improbable that, given the progressive nature of the condition, as seen by neuroimaging, that CBT by itself will be sufficient to prevent onset of full psychosis (Koutsouleris 2009, Meisenzahl 2008, Meisenzahl 2008).

## SAFETY ISSUES

When looking into the side effects of interventions we have excluded studies in which the pharmacological treatment is not specific e.g. Nordentoft et al (Nordentoft 2006) and also those that only provide treatment with CBT. Although theoretically CBT may indeed have some harmful side effects such as increased anxiety at the beginning of treatment as the patient gets used to receiving and making use of therapy, it is not possible to identify from the papers the number of patients who have had untoward side effects as a result of this therapy (Morrison 2002, Morrison 2004, Bechdolf 2007). Furthermore, trials of the use of antidepressants, including trials of the use of antidepressants versus atypical antipsychotics do not contain information about side effects of these pharmacological treatments. They do however illustrate that there is much better compliance with treatment with antidepressants than there is with atypical antipsychotics (Cornblatt 2003, Cornblatt 2007).

The studies which report on harmful side effects in treatment of prodromal psychosis are the ones which report on the use of atypical anti-psychotics, including studies with risperidone, olanzapine, amisulpride, and aripiprazole (McGorry 2002, Woods 2007, McGlashan 2003, McGlashan 2006, Ruhrmann 2007). Of note, the study on aripiprazole has no control group whereas all the others do. Some studies have used low dose antipsychotics e.g. risperidone 1-2mg and others have used higher dose (standard treatment dose) antipsychotics e.g. olanzapine 5-15mg. Hence, the outcomes of the studies may very well be expected to be different.

### Risperidone

In the original McGorry risperidone study using low doses (McGorry 2002) the only reported side effect was stiffness. This developed in 12.9% (31) of the patients in the intervention group.

A further report on the use of risperidone (0.5mg to 2 mg) and CBT has recently been published by Yung (Yung 2011). The aim of the study was to reduce transition to psychotic disorder, and to assess the level of symptoms and functioning in the following different trial groups:

- cognitive therapy + risperidone n = 43;
- cognitive therapy + placebo n = 44;
- supportive therapy + placebo n = 28;
- monitoring group (patients agreed to follow-up assessments but not to randomization into the study) n=78.

This study specifically identified four groups of adverse events:

- psychic e.g. concentration difficulties, increased fatigability and depression;
- neurologic e.g. including dystonia, rigidity and tremor;
- autonomic e.g. accommodation disturbances, orthostatic disturbances and constipation;

- others e.g. sexual side effects, rashes, photosensitivity and headaches.

There was no significant difference between the incidence of any of these groups of symptoms in any of the treatment groups. In particular there was no significant difference in weight gain between the treatment groups (Yung 2011).

Also interestingly this study showed lower than expected rates of transition to psychosis. At 6 months, 8 of the 115 participants in the study (7.0%) and 4 of the monitoring group (5.1%) had developed a psychotic disorder.

### Olanzapine

In the olanzapine study (McGlashan 2003, McGlashan 2006) no significant differences were reported between the treatment groups regarding extrapyramidal symptoms, and in the proportion of patients who had normal baseline ECG results but abnormal post-baseline results.

There were no clinically meaningful changes in laboratory results (McGlashan 2003, McGlashan 2006). It was reported that of 35 laboratory test results which were analyzed, there were no values which were out of the normal range in either group and this included values for blood glucose and cholesterol (McGlashan 2003, McGlashan 2006).

However it was reported that there were significant differences between the two groups for five measures:

- alkaline phosphatase (p=0.02);
- $\gamma$ -glutamyltransferase (p=0.02);
- hematocrit (p=0.04);
- inorganic phosphorus (p=0.03);
- uric acid (p=0.007).

More importantly, the rates of two adverse events related to treatment were significantly different in the two groups. Thus fatigue was reported by 29.0% of the patients in the olanzapine group (9/31) and only by 3.4% of the patients in the placebo group (1/29) (p=0.01) (McGlashan 2003, McGlashan 2006). Furthermore, increased weight was noted by 61.3% of the olanzapine patients (19/31) and 17.2% of the placebo patients (5/29) (p=0.001) (McGlashan 2003, McGlashan 2006). It is of interest that weight gain also occurred in the placebo group.

### Amisulpride

In the amisulpride study the dose was between 50mg and 800mg (Ruhrmann 2007). The study reported on hyperprolactinaemia, extrapyramidal side effects, raised liver enzymes (alanine aminotransferase) and BMI.

Prolactin levels were reported to increase significantly more frequently in the amisulpride-treated group (36/44, 81.8% v. 7/34, 20.6%; P<0.001). The mean relative change from baseline to end-point was reported to be 795.4% in the amisulpride group, but only 47.2% in the group with needs-focused interven-

tion alone ( $P < 0.001$ ) (Ruhrmann 2007). At the end-point, the upper limit of normal was exceeded more than twice by 1 of 31 (3.2%) controls, compared to 29 out of 40 (75.2%) in the amisulpride group who started in the normal range ( $p < 0.001$ ) (Ruhrmann 2007).

It was found that the mean and maximum daily or cumulative doses of amisulpride were not significantly correlated with the percentage elevation of prolactin (Ruhrmann 2007). It was also found that addition of an SSRI to amisulpride (7/44, 3 males, 4 females) was significantly correlated with larger prolactin elevations (Ruhrmann 2007).

Despite the large number of patients whose prolactin was raised, menstrual disturbances occurred transiently in only four women, while another woman developed a prolonged cycle and one other woman dropped out later owing to amenorrhoea (Ruhrmann 2007). In males, two developed erectile and ejaculatory dysfunction and another noted decreased sexual desire and erectile dysfunction (Ruhrmann 2007).

Liver alanine aminotransferase levels more than twice the upper limit of normal were reported in three participants in the amisulpride group (4.9%) (Ruhrmann 2007).

Extrapyramidal symptoms were analysed with respect to the ESRS total score and for the sub-scales 'parkinsonism', 'akathisia', 'dyskinesia' and 'dystonia'. It was found that there were no statistically significant changes from baseline to endpoint in either group for these symptoms (Ruhrmann 2007). When the end point was reached, total scores for these extrapyramidal symptoms ranged from 0 to 5 in the control group and from 0 to 19 in the amisulpride group, while 36 out of 61 (59.0%) in the amisulpride group showed no symptoms and 21 out of 61 (34.4%) exhibited scores of from 1 to 5 (Ruhrmann 2007).

It was observed that there were no statistically significant differences between the two groups with regard to change in scores or scores at the end-point, except for the akathisia end-point scores (amisulpride mean 0.5, controls, mean 0.2,  $P < 0.05$ ) (Ruhrmann 2007). Only 4 of 61 and 1 of 43 participants from the amisulpride and control groups respectively showed the 'presence of akathisia' (Ruhrmann 2007).

Biperiden was prescribed for 3 out of 51 amisulpride-treated participants (Ruhrmann 2007). The daily mean, maximum and end-point doses of amisulpride in these three participants were 239.4, 408.3, and 333.3mg respectively (Ruhrmann 2007).

The BMI increased slightly but significantly in the amisulpride group (mean end-point minus baseline 0.63 (2.6%),  $P < 0.001$ ). There was a significant difference in mean group changes ( $P = 0.001$ ) (Ruhrmann 2007).

### **Aripiprazole**

In the aripiprazole study, the intervention group comprised 15 patients, of which 61.5% developed akathisia (Woods 2007).

## **NUMBERS NEEDED TO HARM**

The difference between very low doses of antipsychotics, as used by McGorry and Yung, compared to using doses within or including the normal therapeutic range as in the olanzapine, amisulpride and aripiprazole studies is shown quite dramatically by calculating the numbers needed to harm. These are reported to the nearest whole figure for the main reported side effects from the studies.

Risperidone nnh=8 for stiffness;  
Olanzapine nnh=2 for weight gain;  
Olanzapine nnh=4 for fatigue;  
Amisulpride nnh=2 for hyperprolactinaemia;  
Aripiprazole nnh=2 for akathisia.

Many more patients need to be treated with low dose antipsychotics (risperidone) to produce the side effect reported than is the case with the other studies using treatment dose antipsychotics. It is evident from the numbers needed to harm that low dose risperidone (plus CBT) is a different modality from anti-psychotics at full dose alone. It should be preferable to use the low dose risperidone modality in treating prodromal psychosis with anti-psychotics when these are indicated. There is urgent need for an evaluation of low doses of other antipsychotics in these patients.

## **PREVENTATIVE PSYCHIATRY: IS IT FEASIBLE?**

In order to decide whether it is appropriate to treat the prodrome it is necessary to assess whether the side effects due to use of the medications outweigh the advantages in terms of preventing development of psychosis and alleviation of symptoms.

The dividing line between the prodrome and first episode of psychosis is humanly determined. In fact the change in intensity of psychotic symptoms, which is mirrored by increasing grey matter loss and hence presumably ongoing damage to the brain is a continual process across the prodromal and first episode stages (Pantelis 2003, Koutsouleris 2009, Meisenzahl 2008, Meisenzahl 2008). Intervention during early phases is to prevent the damage that occurs in the late prodrome, rather than only in the first episode (Singh 2005, Marshall 2005). There are two ways of measuring the progression of psychotic illness either clinical judgement of the degree and intensity of psychotic symptoms e.g using CAARMS or sequential neuroimaging to determine the degree of grey matter loss.

It remains a clinical decision when to treat patient, if patients do not yet clearly demonstrate psychotic symptoms, even attenuated ones, (for example those who have depression and anxiety symptoms only plus a family history of psychosis), then antipsychotic medication is not indicated. Such patients would not be rated as being at ultra-high risk of developing psychosis as rated by an instrument such as CAARMS.

The different side effects reported from the antipsychotics are those which would be expected of these same medications when used with patients which are fully psychotic. A more effective 'cost benefit' analysis of the use of these medications in prodrome could be performed if we knew more about:

- What the lowest effective doses are?
- Whether some of the symptoms referred to as side effects are in fact related to the illness itself.
- What other possible treatments and available and effective?

### Lowest effective dose

The dose of risperidone used and hence advocated by the trials is 0.5-2mg, while the accepted dose for treating fully psychotic patients is 1-6mg. Thus the dose for treating attenuated (prodromal) symptoms is clearly less than that for full psychosis, and this may account for the less severe side effect profile in the risperidone studies than that in the other studies. On the other hand, 5-15mg olanzapine is the dose used in the olanzapine trial, while 10-20mg of olanzapine is the dose licensed for treatment of full psychotic symptoms. The use of a dose of olanzapine which is very similar to the dose for full psychosis may well have influenced the outcome that 61% of patients reported weight gain. Equally 50-800 mg was the dose permitted in the amisulpride study while 800mg is the maximum dose licensed for treating full psychotic illness. This dosage may well have influenced the outcome that 81.8% of patients in the intervention group developed hyperprolactinaemia.

In other words, it is not simply the issue that antipsychotics may cause side effects when used to treat patients in the prodrome of psychosis. Low doses, similar to those in the risperidone studies, need further study to see if this dose dependant relationship is true for different antipsychotics. If it is the case then low doses should be used to treat prodromal 'attenuated' positive symptoms. If doses need to be escalated to doses similar to those used in full psychosis then the possibility needs to be considered that the patient needs to have transitioned into full psychosis. It is incorrect to conclude that the strategy of treating patients with attenuated psychotic symptoms in the prodromal period is wrong if your sources of information rely on inappropriately assessed patients (as to their stage of illness) treated with equally inappropriately high dosages.

### Side effects or symptoms of illness itself

Some of the symptoms referred to as side effects could be related to the development of the illness itself. Weight gain is a side effect traditionally attributed to antipsychotic therapy. It was noted that in the olanzapine study 61% of patients in the intervention group reported weight gain, while in the amisulpride study, 2.6% had a raised BMI. It is of interest however that the latest study using risperidone in low dosage

reports that there was no significant difference in weight gain between the treatment groups.

It has been argued that in schizophrenia, metabolic problems including weight gain and diabetogenesis are part of the general illness itself, and not necessarily only related to the prescribed antipsychotic medication. Antipsychotics can of course exacerbate such weight gain (Olsen 2008, Bernardo 2009, Herken 2008, Verma 2009, Goh 2010). This might explain the lack of difference in weight gain between the three groups, including the placebo, in the risperidone study.

### Alternatives to antipsychotics

The aim in treating these patients is to prevent the development of full psychosis and help them return to full functioning in work or education, and indeed to maintain this full functioning. In order to maintain these patients, who do carry a vulnerability to psychosis, treatment may need to be long term. Agents with fewer side effects and which still have action in modifying processes of apoptosis and changes in plasticity are under consideration (Berger 2007).

Trials have been carried out with omega three fatty acids. These show promise and there are no reports of serious side effects. However these are only of three months duration and one would expect treatment to be needed for longer (Amminger 2010, Amminger 2008).

A first recent trial with lithium has been reported (Berger 2012). Again this shows promise, however lithium therapy involved concerns about toxicity to the thyroid and kidneys, as well as acute toxicity, and therefore does not seem a useful treatment for prodromal patients requiring long term therapy.

Cornblatt has reported treatment with SSRI antidepressants, which are generally considered to have relatively safe side effect profile except the link to increased suicidality in young patients (Cornblatt 2003, Stone 2009). There appears to be better compliance with SSRIs than with antipsychotics in prodromal patients in the reported studies, thus accounting in part at least for the increased effectiveness of the SSRIs. She therefore suggested that in some cases, it may be preferable to begin treatment using antidepressants and to then progress to antipsychotics once symptoms intensify, since adherence to antipsychotics may be difficult to maintain (Cornblatt 2007). Fusar Poli et al have reported similar results (Fusar-Poli 2007). A further study has however failed to demonstrate that antidepressants can reduce positive psychotic symptoms (Walker 2009).

Oestrogens have been used in post menopausal women to augment the effectiveness of antipsychotics (Kulkarni 1996, Kulkarni 2008) however there are no studies in prodromal patients and there are known increased risks of deep vein thrombosis and other clotting disorders linked with oestrogen therapy. There have been no reports of the effectiveness of other possible treatment options in prodromal psychosis.

The use of cognitive therapy alone is generally regarded as safe, and we presently await the outcome of a large scale British study of this form of treatment. There are presently no known side effects, but it remains necessary to establish the efficacy of such treatment in patients who are ultra high risk, and so very close to the development of full psychotic illness.

## STIGMA AND UNNECESSARY TREATMENT

The mention of Cornblatt's and Fusar-Poli's (Fusar-Poli 2007) use of antidepressants as compared to anti-psychotics in the treatment of prodromal psychosis does raise an interesting psychological side effect of treatment of these patients; that of stigma. Patients treated with anti-psychotics will inevitably be aware that they are receiving a treatment for psychotic illness, even though they are not fully psychotic. The knowledge that they require such treatment will give rise to stigma, including self stigmatisation, and it has been suggested that the effectiveness of anti-depressants in treating these patients is in part related to the tendency of the group who were prescribed anti-psychotics not to take the medication prescribed (Cornblatt 2003, Cornblatt 2007).

## CONCLUSION

The present position regarding the treatment of prodromal psychosis is that, whereas the ongoing loss of grey matter as demonstrated by several MRI studies strengthens the case for the necessity of treatment in patients who are at ultra high risk of developing psychosis, the potential treatments all have drawbacks both in terms of side effects and in terms of efficacy. It is necessary to judge the point at which anti-psychotic treatment should be started on the basis of the ongoing development of symptoms in each individual case, weighing the costs in terms of side effects against the potential benefits. While patients with attenuated positive symptoms are still considered prodromal, or 'ultra high risk', it is necessary to use very low doses of anti-psychotic (e.g. 0.5-2mg Risperidone) rather than doses within the usual licensed doses for first episodes (e.g. 5-15mg Olanzapine or 50-800mg Amisulpride), in order to avoid side effects. If such low doses are ineffective in controlling symptoms, then it is likely that conversion to full psychosis has occurred, and treatment should be given according to the licensed dosage for the relevant medications. If patients do not have attenuated psychotic symptoms and only have non-specific depressive or anxiety symptoms, then treatment with SSRIs is appropriate. In all cases where prodromal psychosis is suspected, omega fatty acids and CBT are certainly very good adjuvant treatments, and may in the future be considered appropriate to use by themselves as appropriate treatment, particularly in the early prodrome.

Treatment of prodromal psychosis continues to present a number of risks. The decision to treat judiciously must depend ultimately on the symptoms presented by the individual case.

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## REFERENCES

1. Agius M, Bradley V, Ryan D, Zaman R: *The ethics of identifying and treating psychosis early*. *Psychiatria Danubina* 2008; 20:93-96.
2. Agius M, Kelly C, Zaman R: *Metanalysis of medical and non medical treatments of the prodromal phase of psychotic illness, the so-called at risk mental states*. *European Neuropsychopharmacology* 2008; 18 suppl 4: S441.
3. Amminger GP, Schäfer MR, Papageorgiou K, Klier CM, Cotton SM, Harrigan SM, Mackinnon A, McGorry PD, Berger GE: *Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial*. *Arch Gen Psychiatry* 2010; 67:146-54.
4. Amminger GP, Schafer M, Papageorgiou K, Harrigan S, McGorry PD, Berger G: *Indicated prevention of psychotic disorders with long-chain omega-3 fatty acids: a randomized, placebo-controlled trial*. *Schizophr Res* 2008; 102:S252.
5. Bechdolf A, et al: *"Randomized controlled multicentre trial of cognitive behaviour therapy in the early initial prodromal state: effects on social adjustment post treatment"*. *Early Intervention in Psychiatry* 2007; 1:71-78.
6. Bentall RP, Morrison AP: *More harm than good: The case against neuroleptics to prevent psychosis*. *Journal of Mental Health* 2002; 11:351-356.
7. Berger G, Dell'Olio M, Amminger P, Cornblatt B, Phillips L, Yung A, Yung Y, Berk M, McGorry P: *Neuroprotection in emerging psychotic disorders*. *Early Intervention in Psychiatry* 2007; 1:114-127.
8. Berger GE, Wood SJ, Ross B, Hamer CA, Wellard RM, Pell G, Phillips L, Nelson B, Amminger GP, Yung AR, Jackson G, Velakoulis D, Pantelis C, Manji H, McGorry PD: *Neuroprotective effects of low-dose lithium in individuals at ultra-high risk for psychosis. A longitudinal MRI/MRS study*. *Curr Pharm Des* 2012; 18:570-5.
9. Bernardo M, Canas F, Banegas JR, Casademont J, Riesgo Y, Varela C: *On behalf of the RICAVA StudyGroup Prevalence and awareness of cardiovascular risk factors in patients with schizophrenia: Across-sectional study in a low cardiovascular disease risk geographical area*. *Eur Psychiatry* 2009; 24:431-441.
10. Cornblatt BA, Lencz T, Smith CW, Correll CU, Auther AM, Nakayama E: *"The Schizophrenia Prodrome Revisited: A Neurodevelopmental Perspective"*, *Schizophrenia Bulletin* 2003; 29:633-651.
11. Cornblatt BA, Lencz T, Smith CW, Olsen R, Auther AM, Nakayama E, et al: *Can antidepressants be used to treat the schizophrenia prodrome? Results of a prospective,*

- naturalistic treatment study of adolescents. *J Clin Psychiatry* 2007; 68:546-57.
12. Fusar-Poli P, Valmaggia L, McGuire P: Can antidepressants prevent psychosis? *The Lancet*, 2007; 370: 1746-1748.
  13. Goh C, Agius M: The stress-vulnerability model how does stress impact on mental illness at the level of the brain and what are the consequences? *Psychiatr Danub* 2010; 22:198-202.
  14. Herken H, Erdal M, Aydin N, Sengul C, Karadag F, Barlas O, Akin F: The association of olanzapine-induced weight gain with peroxisome proliferator-activated receptor-gamma2 Pro 12 Alapolyorphism in patients with schizophrenia. *DNA Cell Biol* 2009; 28:515-9.
  15. Holt C, Butler S and Agius M: Early Intervention in the Prodrome of Psychosis CEPiP 2011; 1:30-34.
  16. Kelly C, Hadjinicolaou AV, Holt C, Agius M & Zaman R: Metaanalysis of Medical and Non-Medical Treatments of the Prodromal Phase of Psychotic Illness in At-Risk Mental States. *Psychiatr Danub* 2010; 22 suppl 1:56-62.
  17. Koutsouleris N, Schmitt GJ, Gaser C, Bottlender R, Scheuerecker J, McGuire P, Burgermeister B, Born C, Reiser M, Möller HJ, Meisenzahl EM: Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. *Br J Psychiatry* 2009; 195:218-26.
  18. Kulkarni, J., de Castella, A., Smith, D., Taffe, J., Keks, N., Copolov, D: A clinical trial of the effects of estrogen in acutely psychotic women. *Schizophr Res* 1996; 20:247-252.
  19. Kulkarni J, de Castella A, Fitzgerald PB, Gurvich CT, Bailey M, Bartholomeusz C, Burger H: Estrogen in severe mental illness: a potential new treatment approach. *Arch Gen Psychiatry* 2008; 65:955-60.
  20. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T: Association Between Duration of Untreated Psychosis and Outcome in Cohorts of First-Episode Patients' *Archives of General Psychiatry* 2005; 62:975-983.
  21. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller TJ, Woods SW, et al: The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. I. Study rationale and design. *Schizophr Res* 2003; 61:7-18.
  22. McGlashan TH, Zipursky RB, Perkins D, Addington J, Miller T, Woods SW, et al: "Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis", *Am J Psychiatry* 2006; 163:790–799.
  23. McGorry PD, Yung AR, Phillips LJ, et al: Randomised controlled trial of interventions designed to reduce the risk of progression to first episode psychosis in a clinical sample with sub threshold symptoms *Archives of General Psychiatry* 2002; 59:921-928.
  24. Meisenzahl EM, Koutsouleris N, Bottlender R, Scheuerecker J, Jäger M, Teipel SJ, Holzinger S, Frodl T, Preuss U, Schmitt G, Burgermeister B, Reiser M, Born C, Möller HJ: Structural brain alterations at different stages of schizophrenia: a voxel-based morphometric study. *Schizophr Res* 2008; 104:44-60.
  25. Meisenzahl EM, Koutsouleris N, Gaser C, Bottlender R, Schmitt GJ, McGuire P, Decker P, Burgermeister B, Born C, Reiser M, Möller HJ: Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophr Res* 2008; 102:150-62.
  26. Morrison AP, Bentall RP, Walford FL, Kilcommons A, Knight A, Kreutz M, Lewis SW: "Randomised controlled trial of early detection and cognitive therapy for preventing transition to psychosis in high-risk individuals Study design and interim analysis of transition rate and psychological risk factors", *British Journal of Psychiatry* 2002; 181(suppl. 43): s78-s84.
  27. Morrison AP, French P, Walford L, et al: A randomised controlled trial of cognitive therapy for prevention of psychosis in people at ultra-high risk. *Schizophrenia Research* 2004; 67:7.
  28. Nordentoft M, Thorup A, Petersen L, Øhlenschlaeger J, Melau M, Christensen T, Krapup G, Jorgensen P, Jeppesen P: "Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment", *Schizophrenia Research* 2006; 83:29-40.
  29. Olsen L: The estrogen hypothesis of Schizophrenia implicates glucose metabolism: Association study in three independent samples *BMC Medical Genetics* 2008; 9:39.
  30. Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ, Yung AR, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGuire PK: Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003; 361:281-8.
  31. Ruhrmann S, Bechdolf A, Kühn KU, Wagner M, Schultze-Lutter F, Janssen B, Maurer K, Häfner H, Gaebel W, Möller HJ, Maier W, Klosterkötter J: LIPS study group, "Acute effects of treatment for prodromal symptoms for people putatively in a late initial prodromal state of psychosis", *British Journal of Psychiatry* 2007; 191(suppl. 51):s88-s95.
  32. Singh SP, Cooper JE, Fisher HL, Tarrant CJ, Lloyd T, Banjo J, Corfe S, Jones P: Determining the chronology and components of psychosis onset: The Nottingham Onset Schedule (NOS). *Schizophr Res* 2005; 80:117-30.
  33. Stone M, Laughren T, Jones ML, Levenson M, Holland P C, Hughes A, Hammad TA, Temple R, Rochester G: Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration *BMJ* 2009; 339:b2880.
  34. Verma SK, Subramaniam M, Liew A, Poon LY: Metabolic risk factors in drug-naive patients with first-episode psychosis. *J Clin Psychiatry* 2009; 70:997-1000.
  35. Walker EF, Cornblatt BA, Addington J, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Woods SW, Heinssen R: The relation of antipsychotic and antidepressant medication with baseline symptoms and symptom progression: a naturalistic study of the North American Prodrome Longitudinal Sample. *Schizophr Res* 2009; 115:50-7.
  36. Woods SW, Tully EM, Walsh BC, Hawkins KA, Callahan JL, Cohen SJ, Mathalon DH, Miller TJ, McGlashan TH: "Aripiprazole in the treatment of the psychosis prodrome. An open-label pilot study", *British Journal of Psychiatry* 2007; 191(suppl. 51):s96-s101.
  37. Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ:

*Prediction of psychosis. A step towards indicated prevention of schizophrenia. Br J Psychiatry Suppl* 1998; 172:14-20.

38. Yung AR, Phillips LJ, Nelson B, Francey SM, PanYuen H, Simmons MB, Ross ML, Kelly D, Baker K, Amminger GP,

Berger G, Thompson AD, Thampi A, McGorry PD: *Randomized controlled trial of interventions for young people at ultra high risk for psychosis: 6-month analysis. J Clin Psychiatry* 2011; 72:430-40.

*Correspondence:*

Mark Agius, MD  
SEPT at Weller Wing, Bedford Hospital  
Bedford, Bedfordshire, MK42 9DJ, UK  
E-mail: ma393@cam.ac.uk